2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ZINC IN THE UNITED STATES

Zinc is ubiquitous in the environment, constituting 20–200 ppm (by weight) of the Earth's crust. It is not found as elemental zinc in nature, instead being found mainly as zinc oxide or sphalerite (ZnS). Zinc is released into the environment as the result of mining, smelting of zinc, lead, and cadmium ores, steel production, coal burning, and burning of wastes. Ambient background air concentrations of zinc are generally <1 $\mu g/m^3$. Zinc is found in soils and surficial materials of the contiguous United States at concentrations between <5 and 2,900 mg/kg, with a mean of 60 mg/kg. The zinc background concentrations in surface waters are usually <0.05 mg/L, but can range from 0.002 to 50 mg/L.

Zinc metal is used most commonly as a protective coating of other metals, such as iron and steel. Zinc is also a component of various alloys including those used for die casting as well as brass and bronze. Many zinc alloys may be found in electrical components of household goods. Alloys containing zinc and copper are used to make U.S. one-cent coins. Zinc metal dust is widely used in paint coatings, as a catalyst, and as a reducing and precipitating agent in organic and analytical chemistry.

Exposure of the general population to zinc is primarily by ingestion. The average daily intake of zinc from food in humans is 5.2–16.2 mg zinc/day; assuming a 70-kg average body weight, this corresponds to 0.07–0.23 mg zinc/kg/day. Zinc is widespread in commonly consumed foods, but tends to be higher in those of animal origin, particularly some sea foods. Meat products contain relatively high concentrations of zinc, whereas fruits and vegetables have relatively low concentrations. Other possible pathways for zinc exposure are water and air. Individuals involved in galvanizing, smelting, welding, or brass foundry operations are exposed to metallic zinc and zinc compounds.

2.2 SUMMARY OF HEALTH EFFECTS

Zinc is an essential nutrient for humans and animals that is necessary for the function of a large number of metalloenzymes, including alcohol dehydrogenase, alkaline phosphatase, carbonic anhydrase, leucine aminopeptidase, and superoxide dismutase. Zinc deficiency has been associated with dermatitis, anorexia, growth retardation, poor wound healing, hypogonadism with impaired reproductive capacity,

impaired immune function, and depressed mental function; an increased incidence of congenital malformations in infants has also been associated with zinc deficiency in the mothers. Zinc deficiency may also have an impact on the carcinogenesis of other chemicals, although the direction of the influence seems to vary with the carcinogenic agent. The recommended dietary allowance (RDA) for zinc is 11 mg/day in men and 8 mg/day in women; these correspond to approximately 0.16 mg/kg/day for men and 0.13 mg/kg/day for women. Higher RDAs are recommended for women during pregnancy and lactation (12 mg/day).

The effects of inhalation exposure to zinc and zinc compounds vary somewhat with the chemical form of the zinc compound, but the majority of the effects seen will occur within the respiratory tract. Following inhalation of zinc oxide, and to a lesser extent zinc metal and many other zinc compounds, the most commonly reported effect is the development of "metal fume fever." Metal fume fever is characterized by chest pain, cough, dyspnea, reduced lung volumes, nausea, chills, malaise, and leukocytosis. Symptoms generally appear a few hours after exposure, and are reversible 1–4 days following cessation of exposure. Exposure levels associated with the development of metal fume fever have not been identified, though are generally in the range of 77–600 mg zinc/m^3. Acute experimental exposures of humans to lower concentrations of zinc oxide (14 mg/m^3 for 8 hours or 45 mg zinc/m^3 for 20 minutes) and occupational exposures to low concentrations of zinc (8–12 mg zinc/m^3 for 1–3 hours and 0.034 mg zinc/m^3 for 6–8 hours) did not produce symptoms of metal fume fever.

In contrast, inhalation of high levels of zinc chloride, which is corrosive, generally results in more pronounced damage to the mucous membranes of the respiratory tract without the effects normally seen in metal fume fever. Symptoms of high-concentration zinc chloride exposure include dyspnea, cough, pleuritic chest pain, bilateral diffuse infiltrations, pneumothorax, and acute pneumonitis, resulting from respiratory tract irritation. In many cases, exposure levels for these effects have not been reported, as the exposures were to zinc chloride-containing smoke and were not quantified and the contribution of other components of the smoke cannot be entirely eliminated. However, one study of zinc chloride exposure estimated an exposure level of 1,955 mg zinc/m^3. Similar irritant effects of zinc chloride have been seen in animal studies of lower exposure levels (13–121 mg/m^3) and longer duration (5–100 daily exposures). The effects observed after zinc chloride inhalation are likely due to the caustic nature of zinc chloride, rather than a direct action of the zinc ion.

Nausea has been reported by humans exposed to high concentrations of zinc oxide fumes (300–600 mg/m^3) and zinc chloride (~120 mg/m^3) smoke, as well as following oral exposure to zinc chloride

and zinc sulfate. Other gastrointestinal symptoms reported in cases of excess zinc exposure include vomiting, abdominal cramps, and diarrhea, in several cases with blood. In general, oral exposure levels associated with gastrointestinal effects of zinc have not been reliably reported, but the limited available data suggest that oral concentrations of 910 mg zinc/L or single-dose exposures of ~140–560 mg zinc (acute oral doses of 2–8 mg/kg/day) are sufficient to cause these effects. The noted effects are consistent with gastrointestinal irritation. It is unclear in the majority of human studies whether the gastrointestinal effects seen following zinc inhalation were due to systemic zinc or were the result of direct contact with the gastrointestinal tract following mucociliary clearance of inhaled zinc particles and subsequent swallowing.

Following longer-term exposure to lower doses (~0.5–2 mg zinc/kg/day) of zinc compounds, the observed symptoms generally result from a decreased absorption of copper from the diet, leading to early symptoms of copper deficiency. The most noticeable manifestation of the decreased copper levels is anemia, manifesting as decreased erythrocyte number or decreased hematocrit. High-dose zinc administration has also resulted in reductions in leukocyte number and function. Some studies have also found decreases in high-density lipoprotein (HDL) levels in humans exposed to increased levels of zinc; however, not all studies have confirmed this observation. Long-term consumption of excess zinc may also result in decreased iron stores, although the mechanism behind this effect is not presently clear.

In most cases, dermal exposure to zinc or zinc compounds does not result in any noticeable toxic effects. Zinc oxide is used routinely in topical applications including sunscreens and creams designed to assist in wound healing. However, dermal exposure to zinc chloride, and to a lesser extent other zinc salts, can result in severe skin irritancy, characterized by parakeratosis, hyperkeratosis, inflammatory changes in the epidermis and superficial dermis, and acanthosis of the follicular epithelia.

Available studies have not presented evidence of reproductive or developmental effects in humans or animals following inhalation of zinc compounds. Effects on reproductive or developmental end points have been noted in oral-exposure animal studies, but generally only at very high doses (>200 mg/kg/day).

Available studies of zinc-induced carcinogenic effects in humans and animals following both oral or inhalation exposure have not adequately demonstrated an increase in cancer incidence following long-term exposure to zinc compounds. The EPA currently classifies zinc and compounds as carcinogenicity group D (not classifiable as to human carcinogenicity).

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The primary effects of zinc are the development of metal fume fever and effects of zinc on copper status; a more detailed discussion of these end points follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other health effects.

Metal Fume Fever. Metal fume fever, a well-documented acute disease induced by inhalation of metal oxides, especially zinc, impairs pulmonary function but does not usually progress to chronic lung disease. Symptoms generally appear within a few hours after acute exposure, usually with dryness of the throat and coughing. The most prominent respiratory effects of metal fume fever are substernal chest pain, cough, and dyspnea. The impairment of pulmonary function is characterized by reduced lung volumes and a decreased diffusing capacity of carbon monoxide. Leukocytosis persisting for approximately 12 hours after the fever dissipates is also a common manifestation of metal fume fever. In general, the symptoms of metal fume fever resolve within 1–4 days after cessation of exposure and do not lead to long-term respiratory effects. Inhalation of "ultrafine" zinc oxide particles may also result in metal fume fever, as well as histologic damage and inflammation of the lung periphery.

Exposure levels leading to the development of metal fume fever have been characterized. Minimal changes in forced expiratory flow were observed 1 hour after a 15–30-minute exposure to 77 mg zinc/m^3 as zinc oxide, while at higher levels (300–600 mg/m^3, from 10 minutes to 3 hours), shortness of breath, nasal passage irritation, cough, substernal chest pain, persistent rales of the lung base, and a decreased vital capacity have been reported. Exposure to lower levels of zinc oxide, either for acute (14 mg zinc/m^3 for 8 hours or 45 mg zinc/m^3 for 20 minutes) or chronic (8–12 mg zinc/m^3 for 1–3 hours and 0.034 mg zinc/m^3 for 6–8 hours) duration did not result in the symptoms of metal fume fever. However, analysis by bronchoalveolar lavage of volunteers exposed to zinc oxide for up to 2 hours (mean concentration 16.4 mg zinc/m^3) revealed an increase in levels of the cytokines TNF, IL-6 and IL-8, and increases in the number of polymorphonuclear leukocytes and lymphocytes in the BAL fluid. Thus, it appears that while the precursor events for the development of metal fume fever begin to occur even at very low zinc concentrations, the condition itself does not appear to fully manifest until exposure levels reach much higher (>75 mg/m^3) levels. Similar effects, including decreased ventilation, an inflammatory response, and changes in cytokine levels, have also been seen in animal studies of zinc oxide inhalation.

The exact mechanism behind the development of metal fume fever is not known, but it is believed to involve an immune response to the inhaled zinc oxide. It has been suggested that the zinc oxide causes inflammation of the respiratory tract and the release of histamine or histamine-like substances. In response, an allergen-antibody complex is formed that may elicit an allergic reaction upon subsequent

exposure to the allergen. In response to the allergen-antibody complex, an anti-antibody is formed. The anti-antibody dominates with continued exposure to the zinc oxide, thereby producing a tolerance. When the exposure is interrupted and re-exposure occurs, the allergen-antibody complex dominates, producing an allergic reaction and symptoms of metal fume fever.

Effects on Copper Status. When ingested zinc levels are very high, zinc is believed to inhibit copper absorption through interaction with metallothionein at the brush border of the intestinal lumen. Both copper and zinc appear to bind to the same metallothionein protein; however, copper has a higher affinity for metallothionein than zinc and displaces zinc from metallothionein protein. Copper complexed with metallothionein is retained in the mucosal cell, relatively unavailable for transfer to plasma, and is excreted in the feces when the mucosal cells are sloughed off. Thus, an excess of zinc can result in a decreased availability of dietary copper, and the development of copper deficiency. This fact has been used therapeutically in the treatment of Wilson's Disease. Zinc supplementation is used to substantially decrease the absorption of copper from the diet, which can aggravate the disease.

Copper is incorporated into metalloenzymes involved in hemoglobin formation, carbohydrate metabolism, catecholamine biosynthesis, and cross-linking of collagen, elastin, and hair keratin. The copper-dependent enzymes, which include cytochrome c oxidase, superoxide dismutase, ferroxidases, monoamine oxidase, and dopamine β-monooxygenase, function mainly to reduce molecular oxygen. Excess zinc may alter the levels or activity of these enzymes before the more severe symptoms of copper deficiency, which include anemia and leucopenia, begin to manifest. Numerous studies in humans receiving 40–50 mg supplemental zinc/day (0.68–0.83 mg zinc/kg/day) have reported decreases in erythrocyte superoxide dismutase, mononuclear white cell 5'-nucleotidase, and plasma 5'-nucleotidase activities. While the results from study to study are not always consistent, the available studies of volunteers identify 40–50 mg supplemental zinc/day as the level at which subtle changes in copper-containing enzymes begin to be seen. This effect level is supported by other studies that collectively identify a no-observed-adverse-effect level (NOAEL) of 30 mg supplemental zinc/day for changes in copper-containing enzyme levels in adult men.

Long-term administration (1–8 years) of high zinc levels (2–11.6 mg/kg/day) has caused anemia in humans. However, adequate studies of the chronic effects of lower levels of zinc on copper status in humans are not available. Decreased hemoglobin and hematocrit and the development of anemia have also been observed in animals orally exposed to high zinc doses.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for zinc. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

No inhalation MRLs have been derived for zinc. A number of acute-duration studies of exposed workers have identified metal fume fever as an end point of concern, with effects generally noted at airborne zinc oxide levels of 77–600 mg zinc/m^3 (Blanc et al. 1991; Hammond 1944; Sturgis et al. 1927). However, these occupational studies were not able to adequately control or correct for possible exposure to other compounds, and were therefore not suitable for use in MRL derivation. Animal studies (Amdur et al. 1982; Drinker and Drinker 1928) corroborate the effects observed in humans; however, the studies are generally limited in the methods utilized, and other possible targets of toxicity were not examined. Only one chronic-duration inhalation study in humans was located (Ameille et al. 1992). In this study, exposure levels were not reported; thus, the study could not be used as the basis for the derivation of a chronic-duration MRL. Thus, no chronic-duration inhalation MRL could be derived.

Oral MRLs

An oral acute MRL was not derived for zinc. A number of case reports involving high-dose acute exposure were located (Brandao-Neto et al. 1990a; Callender and Gentzkow 1937; Lewis and Kokan 1998; Murphy 1970); nausea, vomiting, and other signs of gastrointestinal distress were the primary effects noted. However, a great deal of uncertainty exists for these studies, including a lack of accurate assessment of exposure levels and a minimal evaluation of end points. Animal studies of acute-duration oral exposure to zinc are generally limited to studies of mortality (Domingo et al. 1988a; Straube et al. 1980), with the exception of a study in rats that only evaluated effects on the central nervous system (Kozik et al. 1980). As no studies sufficient for derivation of an acute oral MRL were available, no value was derived.

- An MRL of 0.3 mg zinc/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to zinc.

Prolonged oral exposure to zinc has been shown to decrease the absorption of copper from the diet, resulting in the development of copper deficiency. At low doses (~0.7–0.9 mg zinc/kg/day) and intermediate exposure durations (6–13 weeks), the effect is minor and manifests as subclinical changes in copper-sensitive enzymes, such superoxide dismutase (Davis et al. 2000; Fischer et al. 1984; Milne et al. 2001; Yadrick et al. 1989). At higher exposure levels (~2 mg zinc/kg/day) for chronic duration, more severe symptoms of copper deficiency, including anemia, have been reported (Broun et al. 1990; Gyorffy and Chan 1992; Hale et al. 1988; Hoffman et al. 1988; Patterson et al. 1985; Porter et al. 1977; Prasad et al. 1978; Ramadurai et al. 1993; Stroud 1991; Summerfield et al. 1992).

Available intermediate-duration studies have examined the effect of zinc supplementation on sensitive biological indices in humans. A series of two studies (Bonham et al. 2003a, 2003b) evaluated a large number of hematological and immunological parameters as well as several copper-sensitive enzymes (e.g., superoxide dismutase) in healthy men exposed to 0.43 mg supplemental zinc/kg/day, and reported no significant changes resulting from zinc exposure. Studies by three other groups have evaluated exposures in the 0.6–0.8 mg zinc/kg/day range and identified slight but measurable effects. A study in postmenopausal women receiving a total of 53 mg zinc/day (44 mg supplemental zinc/day, or 0.68 mg supplemental zinc/kg/day) (Davis et al. 2000; Milne et al. 2001) reported increases in bone-specific alkaline phosphatase (~25%) and extracellular superoxide dismutase (~15%) levels and decreases in mononuclear white cell 5'-nucleotidase (~30%) and plasma 5'-nucleotidase (~36%) activity. Another study (Fischer et al. 1984) exposed groups of male volunteers to 0.71 mg supplemental zinc/kg/day for

6 weeks; erythrocyte superoxide dismutase (ESOD) activity decreased after 4 weeks in the supplement group and was significantly lower than controls by 6 weeks. In women exposed to 0.83 mg supplemental zinc/kg/day for 10 weeks, ESOD activity declined over the supplementation period and was significantly ($p<0.05$) lower (47% decrease) than pretreatment values at 10 weeks (Yadrick et al. 1989).

While the decrease in ESOD activity reported in the available human studies is noteworthy, it is important to note that other enzymes, including catalase and other forms of superoxide dismutase, also serve to detoxify superoxide within the body. The overall effect of reducing the levels of an isoform of superoxide dismutase on the body's ability to detoxify superoxide radical is therefore uncertain. The subjects in the zinc supplementation studies did not report increased frequencies of clinical signs or symptoms. The other changes in copper status across the studies evaluating zinc supplementation in the 50 mg/day range, such as changes in alkaline phosphatase, mononuclear white cell 5'–nucleotidase, and plasma 5'–nucleotidase activities (Davis et al. 2000; Milne et al. 2001), are generally slight and of questionable clinical and biological significance. The subclinical changes in copper status observed in the intermediate-duration studies of zinc supplementation (Davis et al. 2000; Fischer et al. 1984; Milne et al. 2001; Yadrick et al. 1989) are considered nonadverse effects.

Yadrick et al. (1989) also reported decreased serum ferritin in zinc-supplemented (0.86 mg supplemental zinc/kg/day) premenopausal women. A statistically significant decrease in serum ferritin levels from 36.6 to 28.2 µg/L (23% decrease), was observed. According to the most recent NHANES data (cited in IOM 2000), the median range for serum ferritin levels in menstruating women is 36–40 µg/L, while a value of <12 µg/L represents depleted iron stores. Thus, the subjects in the Yadrick study dropped below the median range for women of their age group, but were still considerably above the level that would represent a depletion of iron stores. This is supported by a lack of reported changes in hemoglobin or hematocrit levels in the study population (Yadrick et al. 1989). In a 90-day study of postmenopausal women exposed to 0.68 mg supplemental zinc/kg/day while living in a metabolic ward (Milne et al. 2001), no changes were reported in serum iron, hematocrit, or percentage of transferrin saturation were observed. However, the study did not evaluate ferritin levels, which are the most sensitive indicator of body iron stores. Other studies that evaluated similar zinc dose levels (Black et al. 1988; Fischer et al. 1984) have not evaluated ferritin levels or other indices of iron status. ATSDR considers the subclinical change in iron stores as indicated by a decrease in serum ferritin levels to be nonadverse.

As it identified the highest NOAEL for effects of zinc exposure, the Yadrick et al. (1989) study was selected as the principal study for MRL derivation. The study identified subclinical changes in copper

status (decreased ESOD levels) and iron status (decreased ferritin levels) in women exposed to 0.83 mg supplemental zinc/kg/day. This exposure level was designated a NOAEL and selected as the point of departure for the derivation of the MRL. The uncertainty factor for MRL derivation was 3, representing uncertainties involving intrahuman variability; a larger factor for sensitive populations was not believed necessary, as women already represent a sensitive population with regards to changes in iron status. The resulting intermediate-duration MRL is 0.3 mg/kg/day.

It should be noted that the MRL is calculated based on the assumption of healthy dietary levels of zinc (and copper), and represents the level of exposure above and beyond the normal diet that is believed to be without an appreciable risk of toxic response. The MRL is based on soluble zinc salts; it is less likely that nonsoluble zinc compounds would have these effects at similar exposure levels.

- The intermediate-duration oral MRL of 0.3 mg zinc/kg/day has been accepted as the chronic oral MRL.

The chronic oral MRL is expected to be without adverse effects when consumed on a daily basis over a long period of time; neither inducing nutritional deficiency in healthy, nonpregnant, adult humans ingesting the average American diet nor resulting in adverse effects from excess consumption. The MRL was not based on a chronic-duration oral study due to a lack of adequate long-term studies in humans and animals. Several studies have reported copper deficiency-induced anemia resulting from longer-term exposure to zinc, either via supplements or other sources (Broun et al. 1990; Gyorffy and Chan 1992; Hale et al. 1988; Hoffman et al. 1988; Patterson et al. 1985; Porter et al. 1977; Prasad et al. 1978; Ramadurai et al. 1993; Stroud 1991; Summerfield et al. 1992); effects generally occurred at estimated exposure levels of approximately 2–10 mg zinc/kg/day. However, the available studies are limited by small numbers of subjects evaluated (often a single individual), limited evaluation of end points, and limited reporting of study results, making them unsuitable for use in the derivation of a chronic-duration MRL.